THE INVENTION OF CLAIMS 20-34 IS NOT OBVIOUS

Claims 20-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kinders et al., U.S. Patent No. 6,221,621 ("Kinders") in view of Perlman et al., 1981, Journal of Experimental Medicine 153:1592-1603 ("Perlman") and Michael et al., 1993, FASEB 7:A375 ("Michael"). The Office Action alleges that Kinders describes a nexus between the presence of C3 protein and the presence of cancer. The Office Action alleges that Kinders describes the detection of C3 and C3b in the urine of cancer patients by an anti-C3 monoclonal antibody. The Office Action alleges that Perlman teaches that C3b(i) constitutes the largest C3 fragment deposited on target cells and that Michael teaches that malignant epithelial cells synthesize C3b(i). The Office Action alleges that given the combined teachings of Kinders, Perlman and Michael that C3b(i) is present on an *in vivo* tumor cell target, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made "to substitute an anti-C3b(i) antibody for the anti-C3 antibody of Kinders for the detection of cancer *in vivo*." For the reasons detailed below, the rejection cannot stand and should be withdrawn.

Neither Kinders, Perlman nor Michael, alone or in combination, teach or suggest the methods of the claimed invention. Kinders describes methods of screening for cancer *in vitro* by detecting the presence of C3 or a C3 related protein (C3rp) in a sample such as a cell or tissue sample, a fecal specimen, a voided urine sample or material extracted from a cervical swab (see, *e.g.*, Kinders at column 4, lines 9-13 and column 11, lines 35-38). As explained below, Kinders does not teach or suggest methods for determining whether cancer is present at a site in an animal by administering to the animal a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i) covalently linked to a second molecule and detecting whether the labeled antibody is concentrated or localized at said site. For reasons discussed in detail below, there is no teaching or suggestion in Kinders to detect cancer *in vivo* by imaging an animal, much less imaging an animal subsequent to the administration of a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i) covalently linked to a second molecule.

Kinders teaches that C3 or C3rp is present in body fluids of a subject having cancer. Kinders teaches that cancer can be detected using an antibody by detecting the presence of C3 or C3rp not only in cell or tissue samples *in vitro*, but also in body fluids such as voided urine. Kinders' teaching that C3 or C3rp can be detected in samples such as voided urine

would signify to one of skill in the art that C3 or C3rp is circulated in the body rather than being exclusively present in cancerous tissues or cells. In fact, Kinders suggests that the production of C3 or C3rp and its release into body fluid by cancers may be serving as a decoy that interferes with the operation of the complement system and permits cancer cells to escape immune surveillance (see Kinders at column 11, lines 58-63). Accordingly, Kinders' teaching that C3 or C3rp is in body fluids and that such soluble C3 or C3rp can be bound by antibody would indicate to one skilled in the art that anti-C3 or anti-C3rp antibody administered *in vivo* may not concentrate or localize on cancer cells. Thus, Kinders does not teach with a reasonable expectation of success the use of an antibody to C3 or C3rp to detect cancer by concentrating or localizing at a cancer site in an animal, much less an anti-C3b(i) antibody.

The deficiencies in Kinders are not cured by Perlman or Michael. Neither Perlman nor Michael teaches or suggests that an anti-C3b(i) antibody administered to an animal will concentrate or localize at a cancerous site in the animal, much less methods for determining that cancer is present at a site in an animal by detecting if a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i) covalently linked to a second molecule is concentrated or localized at said site. In fact, Michael teaches that C3b(i) is detectable only in the supernatant of *in vitro* cultures of the human cervical carcinoma line HeLa S3 and not in the lysates. Thus, Michael teaches that C3b(i) is not deposited on the cell surface of malignant epithelial cells; thus, an anti-C3b(i) antibody would not concentrate or localize on the surface of these cells *in vivo*. Therefore Michael would lead one skilled in the art to reason that such an antibody, if administered, would be bound by the soluble C3b(i) secreted by cells and present in body fluids. Perlmann teaches that erythrocyte bound C3b(i) can interact with both normal and malignant cells *in vitro*. Perlmann does not teach or suggest what is missing in Kinders and Michael, *i.e.*, that an antibody administered to an animal will concentrate or localize at a cancerous site in the animal. Thus, based on such combination of references, a skilled person in the art would not have a suggestion plus a reasonable expectation of success in methods for determining whether cancer is present at a site in an animal by administering to the animal a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i) covalently linked to a second molecule and detecting whether the labeled antibody is concentrated or localized at said site.

The test for obviousness under 35 U.S.C. §103 is an objective one. It is referenced to the person of ordinary skill in the art, not to the specific inventor. The standard of obviousness under 35 U.S.C. §103 is not "obvious to try." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). There must be a reason or suggestion in the art for carrying out the process used, other than the knowledge learned from the applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Prior art references may be combined to render an alleged invention obvious under 35 U.S.C. § 103, but teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984). The suggestion or incentive must be clear and particular; vague and conclusory statements are insufficient to demonstrate a motivation to combine. *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1161 (Fed. Cir. 1999). The fact that the prior art could be modified to achieve the claimed invention is insufficient without a specific showing of motivation to do so. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Care must be exercised not to use the Applicants' disclosure to fill in the gaps in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985). Thus, an Applicants' own teaching in the application in question cannot constitute a proper basis for formulating obviousness rejections; hindsight reconstruction on the basis of an applicants' disclosure is impermissible. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995).

Thus, based upon the present facts, contrary to the allegations in the Office Action, Kinders, Perlman and Michael, in combination, do not render the methods of the claimed invention obvious.

In view of the foregoing, the rejection under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Attorneys for Applicants believe that all of the present claims meet all the requirements for patentability. Withdrawal of all rejections and reconsideration of the amended claims are requested. An allowance is earnestly sought.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-2296.

Respectfully submitted,

Date: January 10, 2003

Geraldine F. Baldwin 31,232
Geraldine F. Baldwin (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures

By: Jennifer J Chheda
Reg No. 46,617

EXHIBIT A

A MARKED UP VERSION OF THE CLAIMS
AMENDED ON JANUARY 10, 2003
IN U.S. APPLICATION SERIAL NO.: 09/392,500
ATTORNEY DOCKET NO.: 9426-019

28. (Once Amended) The method of Claim 20 which further comprises repeating steps (a) through [(d)] (e) at monthly or yearly intervals.

52. (Thrice Amended) The method of Claim [20] 29, 50 or 60 in which the labeled antibody is a human antibody.

EXHIBIT B

PENDING CLAIMS UPON ENTRY OF THE AMENDMENT FILED JANUARY 10, 2003 IN U.S. PATENT APPLICATION SERIAL NO. 09/392,500 ATTORNEY DOCKET NO. 9426-019

20. A method for detecting cancer comprising:

a) administering to an animal an effective amount of a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i) covalently linked to a second molecule;

b) waiting for a time interval following the administration to permit the labeled antibody to concentrate at any cancerous site in the animal;

c) determining background level;

d) detecting the labeled antibody at a site in the animal; and

e) determining that cancer is present at said site in the animal if the labeled antibody is detected above the background level at said site in the animal.

21. The method of Claim 20, 48 or 49 in which the animal is a human.

22. The method of Claim 20, 48, 49, 58 or 59 in which the labeled antibody is a monoclonal antibody.

23. The method of Claim 20, 48, 49, 58 or 59 in which the labeled antibody is a humanized antibody.

24. The method of Claim 20, 48, 49, 58 or 59 in which the labeled antibody is labeled with a radioisotope.

26. The method of Claim 20, 48 or 58 in which time interval is 6 hours to 48 hours.

27. The method of Claim 20, 48, 49, 58 or 59 in which the labeled antibody is administered intravenously.

28. The method of Claim 20 which further comprises repeating steps (a) through (e) at monthly or yearly intervals.

29. A method for detecting cancer in an animal, comprising

(a) imaging said animal at a time interval after administering to said animal an effective amount of a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i) covalently linked to a second molecule, said time interval being sufficient to permit the labeled antibody to concentrate at any cancerous site in said animal; and

(b) determining that cancer is present at a site in said animal if the labeled antibody is localized at said site in the animal.

30. The method of Claim 29 or 50 in which the animal is a human.

31. The method of Claim 29, 50 or 60 in which the labeled antibody is a monoclonal antibody.

32. The method of Claim 29, 50 or 60 in which the labeled antibody is a humanized antibody.

33. The method of Claim 29, 50 or 60 in which the labeled antibody is labeled with a radioisotope.

34. The method of Claim 29, 50 or 60 in which time interval is 6 hours to 48 hours.

48. A method for detecting cancer comprising:

a) administering plasma to an animal;

b) administering an effective amount of a labeled antibody which specifically binds to C3b(i) to said animal;

c) waiting for a time interval following step (b) to permit the labeled antibody to concentrate at any cancerous site in the animal;

d) determining background level; and

e) detecting the labeled antibody in the animal, wherein detection of the labeled antibody above the background level at a site in the animal indicates the presence of a cancer at said site.

49. A method for detecting cancer comprising:

a) administering plasma to an animal;

b) waiting for a time interval following step (a);

c) administering an effective amount of a labeled antibody which specifically binds to C3b(i) to said animal;

d) waiting for a time interval following step (c) to permit the labeled antibody to concentrate at any cancerous site in the animal;

e) determining background level; and

f) detecting the labeled antibody in the animal, wherein detection of the labeled antibody above the background level at a site in the animal indicates the presence of a cancer at said site.

50. A method for detecting cancer in an animal, comprising imaging said animal at a time interval after administrating sequentially to said animal plasma and an effective amount of a labeled antibody which specifically binds to C3b(i), said time interval being sufficient to permit the labeled antibody to concentrate at any cancerous site in said animal, wherein detection of the labeled antibody localized at a site in the animal indicates the presence of cancer at said site.

51. The method of Claim 20, 48, 49, 58 or 59 in which the labeled antibody is a human antibody.

52. The method of Claim 29, 50 or 60 in which the labeled antibody is a human antibody.

53. The method of Claim 48 or 49 in which the plasma is administered intravenously.

55. The method of Claim 48 or 58 which further comprises repeating steps (a) through (e) at monthly intervals.

56. The method of Claim 49 or 59 which further comprises repeating steps (a) through (f) at monthly or yearly intervals.

58. A method for detecting cancer comprising:

a) administering one or more IgM antibodies known to bind to improperly glycosylated cancer cells to a subject;

b) administering an effective amount of a labeled antibody which specifically binds to C3b(i) to said subject;

c) waiting for a time interval following step (b) to permit the labeled antibody to concentrate at any cancerous site in the subject;

d) determining background level; and

e) detecting the labeled antibody in the subject, wherein detection of the labeled antibody above the background level at a site in the subject indicates the presence of a cancer at said site.

59. A method for detecting cancer comprising:

a) administering one or more IgM antibodies known to bind to improperly glycosylated cancer cells to a subject;

b) waiting for a time interval following step (a);

c) administering an effective amount of a labeled antibody which specifically binds to C3b(i) to said subject;

d) waiting for a time interval following step (c) to permit the labeled antibody to concentrate at any cancerous site in the subject;

e) determining background level; and

f) detecting the labeled antibody in the subject, wherein detection of the labeled antibody above the background level at a site in the subject indicates the presence of a cancer at said site.

60. A method for detecting cancer in a subject, comprising imaging said subject at a time interval after administrating sequentially to said subject one or more IgM

antibodies known to bind to improperly glycosylated cancer cells and an effective amount of a labeled antibody which specifically binds to C3b(i), said time interval being sufficient to permit the labeled antibody to concentrate at any cancerous site in said subject, wherein detection of the labeled antibody localized at a site in the subject indicates the presence of cancer at said site.

61. The method of Claim 58 or 59 in which the IgM antibodies known to bind to improperly glycosylated cancer cells are administered intravenously.

62. The method of Claim 58, 59 or 60 in which the subject is a human.